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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/403,844	04/18/1995	OYSTEIN FODSTAD	7885.33USWO	4228

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/403,844	Applicant(s) FODSTAD ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-25,28,29,33-43,46-48,51,59-62,64,66,67,69,71-75 and 78-116* is/are pending in the application.

4a) Of the above claim(s) *41,42,73,74,80-86,90,91,94,95,97-100 and 102-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 40 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims rejected are 22-25,28,29,33-40,43,46-48,51,59-62,64,66,67,69,71,72,75,87-89,92,93,96,101,105,106 and 108-116.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 22-25,28,29,33-43,46-48,51,59-62,64,66,67,69,71-75 and 78-116.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/15/02 has been entered.

Preliminary Amendment Entry

2. Applicant's preliminary amendment filed 2/15/02 in Paper No. 39 is acknowledged and has been entered. Claims 22, 34, 39, 40, 43, 46, 48, 59, 62, 64, 66, 71, 72, 75, 87, 92, 93, 105, 106, 110, 111, and 114-116 have been amended. Claims 78, 79, and 107 have been cancelled. Claim 117 has been added. Accordingly, claims 22-25, 28, 29, 33-43, 46-48, 51, 59-62, 64, 66, 67, 69, 71-75, 80-106, 108-117 are pending. Claims 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 87-89, 92-93, 96, 101, 105-106, and 108-116 are under examination.

Rejection Withdrawn

3. The rejections of claims 78-79 and 107 are now moot in light of Applicant's cancellation of the claims.

4. In light of Applicant's amendment, the rejection of claims 110, 114, and 116 under 35 U.S.C. 112, first paragraph, as containing new subject matter is, hereby, withdrawn.

5. In light of Applicant's amendment, the rejection of claims 22, 46-47, and 106 under 35 U.S.C. 103(a) as being unpatentable over Widder et al. and Connelly et al. (US 5,422,277) in view of Forrest et al. (U.S. Patent 4,659,678), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 46, 88-89, 93, 96, 100 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46, part c) has improper antecedent basis problem in reciting, "a second antibody".

Claim 88 has improper antecedent basis problem in reciting, "A method according to".

Claim 89 has improper antecedent basis problem in reciting, "A method according to".

Claim 93 has improper antecedent basis problem in reciting, "A method according to".

Claim 96 has improper antecedent basis problem in reciting, "A method according to". Claim 96 is indefinite because, it appears that claim 96 should depend from claim 91(or 95) which depends from independent claim 87, and not claim 93.

Claims 101 has improper antecedent basis problems in reciting, "A method according to".

Claim 117 is indefinite in reciting "capable of coating" because it fails to recite a positive limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 22-25, 28-29, 33, 36-38, 48, 51, 59-62, 64, 66, 69, 101, 106, and 108-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. (EP 016,552) in view of Connelly et al. (US 5,422,277) and in further view of Abram et al. (US 4,497,900).

Widder et al. teach a method for separation of select population of cells from a mixed cell population using magnetic particles coated with a layer of specific antibodies which selectively bind to the select population. The coated microspheres with antibodies specific to target cells are contacted with the mixed population and the bound select population is magnetically separated from the mixed population (see page 4, last paragraph). The magnetically responsive microspheres have Protein A associated into the surface which selectively binds antibodies through the Fc region of the antibodies so that Fab arms of the antibodies extend outwardly for binding (see page 4, first paragraph). Widder et al. teach microspheres which are coupled with FITC conjugated rabbit IgG by incubation at 37°C for 20 minutes and examined (see page 10, Example 1). Furthermore, Widder et al. teach using the coated particles to separate red blood cells (RBC) from suspensions containing a mixture of different RBCs. Antibodies were coupled to the microspheres by incubation of 0.5 mg of the microspheres suspended in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate). The RBCs were labeled with 51Cr and incubated with mild agitation and bound microspheres were separated and counted using a gamma counter (see page 11, Example 2).

The method of Widder et al differs from the instant invention in failing to teach incubation of the antibody coated microspheres in mild detergent for 5-10 minutes to 2 hours at 4°C. Furthermore, Widder fails to teach the use of an antibody to immobilize antibodies on the surface of the magnetic particles.

Connelly et al. teach various fixatives used to fix cells without destroying cellular properties. Connelly et al. specifically teach fixing cells with phosphate buffer solution followed by DMSO and DNBS, TweenTM (polyethylene sorbitans monolaurate - Tween 20 or monooleate - Tween 80) and formaldehyde (see column 9, lines 10-14) and then incubating the cells for 20 minutes to 2 hours at temperatures ranging from 0°C to 37°C (see column 9, lines 20-48).

It would have been obvious to one of ordinary skill in the art to use detergents to treat cells as used by Connelly following certain specific temperature and time parameters because the use detergents to treat cells is well known and conventional in the art for removing extraneous matter from the cells that will interfere with assays. One of ordinary skill in the art would have been motivated to incorporate Connelly's fixative techniques and parameters in Widder separation method because Connelly specifically states that one of ordinary skill in the art of cell fixation may routinely have to vary the aforementioned cell treatment parameters as in Widder's RBCs (dependent on cellular type) in order to obtain desired cell fixation without substantial destruction of cellular properties.

Widder et al. and Connelly et al. fail to teach that a first antibody coated to the paramagnetic particle is directed against a second antibody or antibody fragment that is directed against a cell membrane structure.

Abram et al. disclose an immunoassay for determining the presence of antigen wherein antigen-antibody complexes comprising antigen and antibodies (second antibody) are further incubated (treated) with a primary antibody (first antibody=antiglobulin). Specifically, the primary antibody is directed against the secondary antibody that is bound to the antigen.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use antibodies directed to other antibodies such as taught by Abram to immobilize other antibodies on the surface of the magnetic particles in the method of Widder and Connelly because Abram specifically taught that a primary antibody directed against a secondary antibody can be used for binding two elements to form complexes, such as a label to an antigen (label -1° antibody- 2° antibody - analyte complexes) or a paramagnetic bead to a cell surface antigen (paramagnetic bead - 1° antibody - 2° antibody - cell surface antigen complexes) and Widder specifically has shown that immobilizing specific antibodies on a surface of a solid support, such as magnetic particles is conventional and well within ordinary skill.

In addition, given the combined teaching of Widder, Connelly, and Abram, the sensitivity levels recited in claims 62, 110, 114, and 116 appear to be achieved by optimization procedures. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a

result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). Since Applicant has not disclosed that the specific limitations recited in instant claims 62, 110, 114, and 116 are for any particular purpose or solve any stated problem and the combined teachings of the prior art appears to suggest the claimed invention; absent evidence to the contrary, it would have been obvious for one of ordinary skill to discover the optimum workable value achieved by the methods disclosed in the prior art by normal optimization procedures.

8. Claims 22, 46-48, and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Connelly et al. (US 5,422,277), in further view of Abram et al. (US 4,497,900), and in further view of Forrest et al. (U.S. Patent 4,659,678).

Widder et al. and Connelly et al. fail to teach that the first antibody is directed against a second antibody or antibody fragment that is directed against a cell membrane structure.

Abram et al. has been discussed supra. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Abram of antibodies directed to other antibodies and immobilize these antibodies on the surface of magnetic particles in the method taught by Widder and modified by Connelly, because Abram specifically taught that a primary antibody directed against a secondary

antibody can be used for binding two elements to form complexes, such as a label to an antigen (label -1° antibody- 2° antibody - analyte complexes) or a paramagnetic bead to a cell surface antigen (paramagnetic bead - 1° antibody - 2° antibody - cell surface antigen complexes) and Widder specifically taught that immobilizing specific antibodies on a surface of a solid support, such as magnetic particles is conventional and well known in the art.

Widder et al., Connelly et al., and Abram et al. have been discussed supra. The methods of Widder et al., Connelly et al., and Abram et al. differ from the instant invention in failing to incorporate the antibodies, buffers, and reagent into a kit format.

Forrest et al teach a sandwich assay wherein a complex is formed between antigen in a sample and two or more antibody reagents and bound to solid supports such as magnetic or paramagnetic particles or beads having labeled or unlabeled antibodies attached thereto (see Abstract, column 1 and 2). The label employed may be selected from those known in the art such as fluorimetric or enzyme labeling. Forrest et al. teach using Protein A attached to the solid support and further attached to an antibody (see column 3-4). Forrest et al. teach using antibody reagents (which constitute intact antibodies or fragments thereof) that constitute a specific binding protein such as avidin and biotin and adding the reagents in any order so as to optimize the reaction conditions (column 5).

It would also have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the antibodies, buffers, beads, and reagent in the methods of Widder et al., Connelly et al., and Abram et al. in a test kit arrangement

such as taught by Forrest because test kits are conventional and well known in the art for their recognized advantages of convenience and economy.

9. Claims 34-35, 39-40, 43, 71-72, 75, 87-89, 92-93, 96, and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. (EP 016,552) in view of Connelly et al. (US 5,422,277) and in further view of Abram et al. (US 4,497,900) as applied to claims 22-25, 28-29, 33, 36-38, 48, 51, 59-62, 64, 66, 69, 80, 82-86, 99, 101-106, and 108-115 above, and further in view of Kemmer et al. (Journal of Immunological Methods, 1992) and Holmes et al. (WO 91/09938).

Widder et al. and Connelly et al. fail to teach that the first antibody is directed against a second antibody or antibody fragment that is directed against a cell membrane structure.

Abram et al. has been discussed supra. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate antibodies directed to other antibodies such as taught by Abram for immobilizing other antibodies on the surface of magnetic particles into a method such as taught by Widder and modified by Connelly because Abram specifically taught that a primary antibody directed against a secondary antibody can be used for binding two elements to form complexes, such as a label to an antigen (label -1° antibody- 2° antibody - analyte complexes) or a paramagnetic bead to a cell surface antigen (paramagnetic bead - 1° antibody - 2° antibody - cell surface antigen complexes) and Widder specifically taught

that immobilizing specific antibodies on a surface of a solid support, such as magnetic particles is conventional and well known in the art.

Widder et al., Connelly et al., and Abram et al. have been discussed supra. The methods of Widder et al., Connelly et al., and Abram differ from the instant invention in failing to teach separation and detection of specific cells, in this case, cancer cells.

Kemmer et al. teach isolation of tumor cells from a mixed cell suspension of human tumor tissue which contains tumor cells, leucocytes, and erythrocytes, using magnetic beads coated with monoclonal antibodies.

Holmes et al. teach a method of separating hematopoietic progenitor cells from a mixed population of hematopoietic cells which contain malignant cells using microbeads coated with murine antibody which binds to the Fc portion of IgG murine antibodies or Protein A which reacts universally with the Fc portion of virtually all IgG antibodies (see page 6, lines 8-24). The mixed population of Holmes et al. is commonly derived from the bone marrow mononuclear cells, fetal, and umbilical cord blood or adult human blood.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the method of cell separation taught by Widder, as modified by Connelly and Abram, to separate cells from a variety of cell samples as taught by Kemmer and Holmes because Kemmer and Holmes teach that it is advantageous to remove tumor cells from a mixed population using magnetic microbeads coated with either monoclonal antibodies or protein A for the purpose of further studying the tumor cells or to purge a sample of tumor cells. The use of various monoclonal antibodies

specific for antigens present on the cell surface for binding, separation, and detection is well known in the art and a skilled artisan would have had a reasonable expectation of success in choosing an antibody that is specific for an antigen present on the surface if the cell population of interest.

10. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Connelly et al. (US 5,422,277), in further view of Abram et al. (US 4,497,900), and in further view of Kemmer et al. (Journal of Immunological Methods, 1992) and Forrest et al. (U.S. Patent 4,659,678).

Widder et al., Connelly et al., Abram et al., and Kemmer et al. have been discussed supra. The methods of Widder et al., Connelly et al., Abram et al., and Kemmer et al. differ from the instant invention in failing to incorporate the antibodies, beads, buffers, and reagent into a kit format.

Forrest et al. has been discussed supra.

It would also have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the antibodies, buffers, beads, and reagent in the methods of Widder and modified by Connelly, Abram, Kemmer into a test kit arrangement such as taught by Forrest because test kits are conventional and well known in the art for their recognized advantages of convenience and economy.

Response to Arguments

11. A) Applicant argues that the combination of Widder and Connelly with Forrest does not suggest the teaching of the claimed invention. Applicant argues that claims including claims 46-47 and 106 provide a method and kit for detecting target cells where antibodies that recognize cell membrane structures are not directly bound to the paramagnetic particles. Instead the paramagnetic particles are coated with antibodies which are directed against primary antibodies that recognize cell membrane structures in target cells wherein the primary antibodies are first incubated with the cell suspension containing the target cells and washed prior to contacting with the coated paramagnetic particles.

In response, the feature by which Applicant relies, i.e. the paramagnetic particles are coated with antibodies which are directed against primary antibodies that recognize cell membrane structures in target cells, was not previously recited in the rejected claims. However, Applicant has amended claims 46-47 and 106 to recite such features; therefore, the rejection has been withdrawn.

B) Applicant argues that the combination of Widder, Connelly, and Abram fails to suggest the teaching of the claimed invention. Specifically, Applicant argues that Widder and Connelly fail to teach paramagnetic beads which are coated with (first) antibodies directed against (second) antibodies that are directed against cell surface antigens. Applicant argues that Widder fails to teach incubation of antibody coated microspheres in mild detergent at 4C for 5-10 minutes to 2 hours. Applicant then argues that Abram fails to cure the deficiencies of Widder and Connelly in teaching a

solid phase immunoassay wherein antigen is released from lysed bacteria and immobilized onto a plastic bead.

In response to applicant's arguments against each of Widder, Connelly, and Abram individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, the rejection is based on the combination of the teachings of Widder, Connelly, and Abram as follows. Widder discloses magnetic particles which have protein A in the surface onto which a layer of antibodies are coated and the antibodies selectively bind to a target population of cells. Protein A selectively binds antibodies through the Fc region of the antibodies so that Fab arms of the antibodies extend outwardly for binding. Connelly is incorporated for teaching various fixatives used to fix cells without destroying cellular properties, i.e. polyethylene sorbitans monolaurate – (Tween 20 or monooleate - Tween 80), then incubating the cells for 20 minutes to 2 hours at temperatures ranging from 0°C to 37°C. Abram is further incorporated for teaching an immunoassay configuration wherein antigen-antibody complexes are incubated (treated) with a primary antibody wherein the primary antibody is directed against the antibody that is bound to the antigen. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use antibodies directed to other antibodies such as taught by Abram for immobilization into magnetic particles such as in the method of Widder and modified by Connelly because

Abram specifically taught that a primary antibody directed against a secondary antibody can be used for binding two elements to form complexes, such as a label to an antigen (label -1° antibody- 2° antibody - analyte complexes) or a paramagnetic bead to a cell surface antigen (paramagnetic bead - 1° antibody - 2° antibody - cell surface antigen complexes) and Widder specifically has shown that immobilizing specific antibodies on a surface of a solid support, such as magnetic particles is conventional and well within ordinary skill.

C) Applicant argues that the combination of Widder, Connelly, and Abram with Kemmer or Holmes fails to suggest the teaching of the claimed invention. Specifically, Applicant argues that Widder and Connelly fail to teach paramagnetic beads which are coated with (first) antibodies directed against (second) antibodies that are directed against cell surface antigens. Applicant argues that Widder fails to teach incubation of antibody coated microspheres in mild detergent at 4C for 5-10 minutes to 2 hours. Applicant then argues that Abram teaches away from the claimed invention in teaching a solid phase immunoassay wherein antigen is released from lysed bacteria and immobilized onto a plastic bead. Applicant then argues that Kemmer and Homes fail to cure the deficiencies of Widder, Connelly, and Abram.

In response to applicant's arguments against each of Widder, Connelly, and Abram individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, the rejection is based on the combination of the teachings of Widder, Connelly, Abram, and in further combination with teaching of Kemmer and Holmes as follows. Widder discloses magnetic particles which have protein A in the surface onto which a layer of antibodies are coated and the antibodies selectively bind to a target population of cells. Protein A selectively binds antibodies through the Fc region of the antibodies so that Fab arms of the antibodies extend outwardly for binding. Connelly is incorporated for teaching various fixatives used to fix cells without destroying cellular properties, i.e. polyethylene sorbitans monolaurate – (Tween 20 or monooleate - Tween 80), then incubating the cells for 20 minutes to 2 hours at temperatures ranging from 0°C to 37°C. Abram is further incorporated for teaching an immunoassay configuration wherein antigen-antibody complexes are incubated (treated) with a primary antibody wherein the primary antibody is directed against the antibody that is bound to the antigen. Kemmer is incorporate, thereto, for teaching isolation of tumor cells from a mixed cell suspension, using magnetic beads coated with monoclonal antibodies. Alternatively, Holmes is incorporate, thereto, for teaching separation of hematopoietic progenitor cells from a mixed population which contain malignant cells using microbeads coated with murine antibody which binds to the Fc portion of IgG murine antibodies or Protein A which reacts universally with the Fc portion of virtually all IgG antibodies. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the method of cell separation taught by Widder,

as modified by Connelly and Abram, to separate cancer cells from a heterogeneous cell mixture as taught by Kemmer and Holmes, because Kemmer and Holmes teach that it is advantageous to enrich tumor cells from a mixed population using magnetic microbeads coated with either monoclonal antibodies or protein A for better isolation and identification of tumor cells, just as suggested by the combination of the methods of Widder, Connelly, and Abram.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

5/3/07

Christopher L Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641